3. RISK ASSESSMENT

This section describes the methods used to estimate ambient water quality criteria (AWQC) for the protection of human health for carcinogenic chemicals (Section 3.1) and for noncarcinogenic chemicals (Section 3.2).

3.1   CANCER EFFECTS

3.1.1   Background on EPA Cancer Risk Assessment Guidelines

The current EPA *Guidelines for Carcinogen Risk Assessment* were published in 1986 (USEPA, 1986a, hereafter the "1986 cancer guidelines"). The 1986 cancer guidelines categorize chemicals into alpha-numerical Groups: A, known human carcinogen (sufficient evidence from epidemiological studies or other human studies); B, probable human carcinogen (sufficient evidence in animals and limited or inadequate evidence in humans); C, possible human carcinogen (limited evidence of carcinogenicity in animals in the absence of human data); D, not classifiable (inadequate or no animal evidence of carcinogenicity); and E, evidence of noncarcinogenicity for humans (no evidence of carcinogenicity in at least two adequate animal tests in different species or in both adequate epidemiological and animal studies). Within Group B there are two subgroups, Groups B1 and B2. Group B1 is reserved for agents for which there is limited evidence of carcinogenicity from epidemiological studies. Group B2 is generally for agents for which there is sufficient evidence from animal studies and for which there is inadequate evidence or no data from epidemiological studies (USEPA, 1986). The system was similar to that used by the International Agency for Research on Cancer (IARC).

The 1986 cancer guidelines include guidance on what constitutes sufficient, limited, or inadequate evidence. In epidemiological studies, sufficient evidence indicates a causal relationship between the agent and human cancer; limited evidence indicates that a causal relationship is credible, but that alternative explanations, such as chance, bias, or confounding, could not adequately be excluded; inadequate evidence indicates either lack of pertinent data, or a causal interpretation is not credible. In general, although a single study may be indicative of a cause-effect relationship, confidence in inferring a causal association is increased when several independent studies are concordant in showing the association. In animal studies, sufficient evidence includes an increased incidence of malignant tumors or combined malignant and benign tumors:

- In multiple species or strains;

- In multiple experiments (e.g., with different routes of administration or using different dose levels);

- To an unusual degree in a single experiment with regard to high incidence, unusual site or type of tumor, or early age at onset;

- Additional data on dose-response, short-term tests, or structural activity relationships.

In the 1986 cancer guidelines, hazard identification and the weight-of-evidence process focus on tumor findings. The weight-of-evidence approach for making judgments about cancer hazard analyzes human and animal tumor data separately, then combines them to make the overall conclusion about potential human carcinogenicity. The next step of the hazard analysis is an evaluation of supporting evidence (e.g., mutagenicity, cell transformation) to determine whether the overall weight-of-evidence conclusion should be modified.

For cancer risk quantification, the 1986 cancer guidelines recommend the use of linearized multistage model (LMS) as the only default approach. The 1986 cancer guidelines also mention that a low-dose extrapolation model other than the LMS might be considered more appropriate based on biological grounds. However, no guidance is given in choosing other approaches. The 1986 cancer guidelines recommended the use of body weight raised to the 2/3 power ($BW^{2/3}$) as a dose scaling factor between species.

3.1.2 EPA's Proposed Guidelines for Carcinogen Risk Assessment and the Subsequent July, 1999 Draft Revised Cancer Guidelines

In 1996, EPA published *Proposed Guidelines for Carcinogen Risk Assessment* (USEPA, 1996a, hereafter the "1996 proposed cancer guidelines"). After the publication of the 1996 proposed cancer guidelines and a February, 1997 and January, 1999 Science Advisory Board (SAB) review, a revision was made in July, 1999 *Guidelines for Carcinogen Risk Assessment - Review Draft* (hereafter the "1999 draft revised cancer guidelines"; USEPA, 1999a), and an SAB meeting was convened to review this revised document. When final guidelines are published, they will replace the 1986 cancer guidelines. These revisions are designed to ensure that the Agency's cancer risk assessment methods reflect the most current scientific information and advances in risk assessment methodology.

In the meanwhile, the 1986 guidelines are used and extended with principles discussed in the 1999 draft revised cancer guidelines. These principles arise from scientific discoveries concerning cancer made in the last 15 years and from EPA policy of recent years supporting full characterization of hazard and risk both for the general population and potentially sensitive groups such as children. These principles are incorporated in recent and ongoing assessments such as the reassessment of dioxin, consistent with the 1986 guidelines. Until final guidelines are published, information is presented to describe risk under both the 1986 guidelines and 1999 draft revisions.

The 1999 draft revised cancer guidelines call for the full use of all relevant information to convey the circumstances or conditions under which a particular hazard is expressed (e.g., route, duration, pattern, or magnitude of exposure). They emphasize understanding the mode of action (MOA) whereby the agent induces tumors. The MOA underlies the hazard assessment and provides the rationale for dose-response assessments.

The key principles in the 1999 draft revised cancer guidelines include:

a)   Hazard assessment is based on the analysis of all biological information rather than just tumor findings.

b)   An agent's MOA in causing tumors is emphasized to reduce the uncertainty in describing the likelihood of harm and in determining the dose-response approach(es).

c)   The 1999 draft revised cancer guidelines emphasize the conditions under which the hazard may be expressed (e.g., route, pattern, duration and magnitude of exposure). Further, the guidelines call for a *hazard characterization* to integrate the data analysis of all relevant studies into a weight-of-evidence conclusion of hazard and to develop a working conclusion regarding the agent's mode of action in leading to tumor development.

d)   A weight-of-evidence narrative with accompanying descriptors (listed in Section 3.1.3.1 below) would replace the current alphanumeric classification system. The narrative summarizes the key evidence for carcinogenicity, describes the agent's MOA, characterizes the conditions of hazard expression, including route of exposure, describes any disproportionate effects on subgroups of the human population (e.g., children), and recommends appropriate dose-response approach(es). Significant strengths, weaknesses, and uncertainties of contributing evidence are also highlighted.

e)   Biologically based extrapolation models are the preferred approach for quantifying risk. These models integrate data and conclusions about events in the carcinogenic process throughout the dose-response range from high to low doses. It is anticipated, however, that the necessary data for the parameters used in such models will not be available for most chemicals. The 1999 draft revised cancer guidelines allow for alternative quantitative methods, including several default approaches.

f)   Dose-response assessment is a two-step process. In the first step, response data are modeled in the observable range of data and a determination is made of the point of departure (POD) from the observed range to extrapolate to low doses. The second step is extrapolation from the POD to estimate dose-response at lower doses. In addition to modeling tumor data, the 1999 draft revised cancer guidelines call for the use and modeling of other kinds of responses if they are considered to be more informed measures of carcinogenic risk. Nominally, these responses reflect key events in the carcinogenic process integral to the MOA of the agent.

g)   Three default approaches are provided–linear, nonlinear, or both when adequate data are unavailable to generate a biologically based model. As the first step for all approaches, curve fitting in the observed range is used to determine a POD. A standard POD is the effective dose corresponding to the lower 95 percent limit on a dose associated with 10 percent extra risk (LED_{10}).[3] *Linear*: The linear default is a straight line extrapolation from the response at LED_{10} to the origin (zero dose, zero extra risk). *Nonlinear*: The nonlinear default begins with the identified POD and provides a margin of exposure (MOE) analysis rather than estimating the probability of effects at low doses. The MOE analysis is used to determine the appropriate margin between the POD and the exposure level of interest, in this Methodology, the AWQC. The key objective of the MOE analysis is to describe for the risk manager how rapidly responses may decline with dose. Other factors are also considered in the MOE analysis (i.e., nature of the response, slope of the dose-response curve, human sensitivity compared with experimental animals, nature and extent of human variability in sensitivity and human exposure). *Linear and nonlinear*: Section 3.1.3.4E describes the situations when both linear and nonlinear defaults are used.

h)   The approach used to calculate an oral human equivalent dose when assessments are based on animal bioassays has been refined and includes a change in the default assumption for interspecies dose scaling. The 1999 draft revised cancer guidelines use body weight raised to the 3/4 power.

EPA health risk assessment practices for both cancer and noncancer endpoints are beginning to come together with recent proposals to emphasize MOA understanding in risk assessment and to model response data in the observable range to derive PODs for data sets and benchmark doses (BMDs) for individual studies. The modeling of observed response data to identify PODs in a standard way will help to harmonize cancer and noncancer dose-response approaches and permit comparisons of cancer and noncancer risk estimates.

3.1.3   Methodology for Deriving AWQC[4] by the 1999 Draft Revised Cancer Guidelines

Following the publication of the *Draft Water Quality Criteria Methodology: Human Health* (USEPA, 1998a) and the accompanying TSD (USEPA, 1998b), EPA received comments from the public. EPA also held an external peer review of the draft Methodology. Both the peer reviewers and the public recommended that EPA incorporate the new approaches into the AWQC Methodology.

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[3] Use of the LED_{10} as the point of departure is recommended with this Methodology, as it is with the 1999 draft revised cancer guidelines.

[4] Additional information regarding the revised method for assessing carcinogens may be found in the *Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health (2000). Technical Support Document*, *Volume 1: Risk Assessment* (USEPA, 2000).

Until new guidelines are published, the 1986 cancer guidelines will be used along with principles of the 1999 draft revised cancer guidelines. The 1986 guidelines are the basis for IRIS risk numbers which were used to derive the current AWQC. Each new assessment applying the principles of the 1999 draft revised cancer guidelines will be subject to peer review before being used as the basis of AWQC.

The remainder of Section 3 illustrates the methodology for deriving numerical AWQC for carcinogens applying the 1999 draft revised cancer guidelines (USEPA, 1999a). This discussion of the revised methodology for carcinogens focuses primarily on the quantitative aspects of deriving numerical AWQC values. It is important to note that the cancer risk assessment process outlined in the 1999 draft revised cancer guidelines is not limited to the quantitative aspects. A numerical AWQC value derived for a carcinogen is to be based on appropriate hazard characterization and accompanied by risk characterization information.

This section contains a discussion of the weight-of-evidence narrative, that describes all information relevant to a cancer risk evaluation, followed by a discussion of the quantitative aspects of deriving numerical AWQC values for carcinogens. It is assumed that data from an appropriately conducted animal bioassay or human epidemiological study provide the underlying basis for deriving the AWQC value. The discussion focuses on the following: (1) the weight-of-evidence narrative; (2) general considerations and framework for analysis of the MOA; (3) dose estimation; (4) characterizing dose-response relationships in the range of observation and at low, environmentally relevant doses; (5) calculating the AWQC value; (6) risk characterization; and (7) use of Toxicity Equivalent Factors (TEF) and Relative Potency Estimates. The first three topics encompass the quantitative aspects of deriving AWQC for carcinogens.

3.1.3.1 <u>Weight-of-Evidence Narrative</u>[5]

The 1999 draft revised cancer guidelines include a weight-of-evidence narrative that is based on an overall judgment of biological and chemical/physical considerations. Hazard assessment information accompanying an AWQC value for a carcinogen in the form of a weight-of-evidence narrative is described in the footnote. Of particular importance is that the weight-of-evidence narrative explicitly provides adequate support based on human studies, animal bioassays, and other key evidence for the conclusion whether the substance is or is likely to be carcinogenic to humans from exposures through drinking water and/or fish ingestion. The Agency emphasizes

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[5] The weight-of-evidence narrative is intended for the risk manager, and thus explains in nontechnical language the key data and conclusions, as well as the conditions for hazard expression. Conclusions about potential human carcinogenicity are presented by route of exposure. Contained within this narrative are simple likelihood descriptors that essentially distinguish whether there is enough evidence to make a projection about human hazard (i.e., Carcinogenic to humans; Likely to be carcinogenic to humans; Suggestive evidence of carcinogenicity but not sufficient to assess human carcinogenic potential; Data are inadequate for an assessment of human carcinogenic potential; and Not likely to be carcinogenic to humans). Because one encounters a variety of data sets on agents, these descriptors are not meant to stand alone; rather, the context of the weight-of-evidence narrative is intended to provide a transparent explanation of the biological evidence and how the conclusions were derived. Moreover, these descriptors should not be viewed as classification categories (like the alphameric system), which often obscure key scientific differences among chemicals. The new weight-of-evidence narrative also presents conclusions about how the agent induces tumors and the relevance of the mode of action to humans, and recommends a dose-response approach based on the MOA understanding (USEPA, 1996a, 1999a).

the importance of providing an explicit discussion of the MOA for the substance in the weight-of-evidence narrative if data are available, including a discussion that relates the MOA to the quantitative procedures used in the derivation of the AWQC.

3.1.3.2   Mode of Action - General Considerations and Framework for Analysis

An MOA is composed of key events and processes starting with the interaction of an agent with a cell, through operational and anatomical changes, resulting in cancer formation. "Mode" of action is contrasted with "mechanism" of action, which implies a more detailed, molecular description of events than is meant by MOA.

Mode of action analysis is based on physical, chemical, and biological information that helps to explain key events[6] in an agent's influence on development of tumors. Inputs to MOA analysis include tumor data in humans, animals, and among structural analogues as well as the other key data.

There are many examples of possible modes of carcinogenic action, such as mutagenicity, mitogenesis, inhibition of cell death, cytotoxicity with reparative cell proliferation, and immune suppression. All pertinent studies are reviewed in analyzing an MOA, and an overall weighing of evidence is performed, laying out the strengths, weaknesses, and uncertainties of the case as well as potential alternative positions and rationales. Identifying data gaps and research needs is also part of the assessment.

Mode of action conclusions are used to address the question of human relevance of animal tumor responses, to address differences in anticipated response among humans such as between children and adults or men and women, and as the basis of decisions about the anticipated shape of the dose-response relationship.

In reaching conclusions, the question of "general acceptance" of an MOA will be tested as part of the independent peer review that EPA obtains for its assessment and conclusions.

Framework for Evaluating a Postulated Carcinogenic Mode(s) of Action

The framework is intended to be an analytic tool for judging whether available data support a mode of carcinogenic action postulated for an agent and includes nine elements:

1. Summary description of postulated MOA
2. Identification of key events
3. Strength, consistency, specificity of association
4. Dose-response relationship
5. Temporal relationship

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[6]A "key event" is an empirically observable, precursor step that is itself a necessary element of the mode of action, or is a marker for such an element.

6. Biological plausibility and coherence
7. Other modes of action
8. Conclusion
9. Human relevance, including subpopulations

3.1.3.3 Dose Estimation

A. Determining the Human Equivalent Dose by the Oral Route

An important objective in the dose-response assessment is to use a measure of internal or delivered dose at the target site where possible. This is particularly important in those cases where the carcinogenic response information is being extrapolated to humans from animal studies. Generally, by the oral exposure route, the measure of a dose provided in the underlying human studies or animal bioassays is the applied dose, typically given in terms of unit mass per unit body weight per unit time, (e.g., mg/kg-day). When animal bioassay data are used, it is necessary to make adjustments to the applied dose values to account for differences in toxicokinetics between animals and humans that affect the relationship between applied dose and delivered dose at the target organ.

In the estimation of a human equivalent dose, the 1999 draft revised cancer guidelines recommend that when adequate data are available, the doses used in animal studies can be adjusted to equivalent human doses using toxicokinetic information on the particular agent. However, in most cases, there are insufficient data available to compare dose between species. In these cases, the estimate of a human equivalent dose is based on science policy default assumptions. To derive an equivalent human oral dose from animal data, the default procedure in the 1999 draft revised cancer guidelines is to scale daily applied oral doses experienced for a lifetime in proportion to body weight raised to the 3/4 power ($BW^{3/4}$). The adjustment factor is used because metabolic rates, as well as most rates of physiological processes that determine the disposition of dose, scale this way. Thus, the rationale for this factor rests on the empirical observation that rates of physiological processes consistently tend to maintain proportionality with body weight raised to 3/4 power (USEPA, 1992a, 1999a).

The use of $BW^{3/4}$ is a departure from the scaling factor of $BW^{2/3}$ that was based on surface area adjustment and was included in the 1980 AWQC National Guidelines as well as the 1986 cancer guidelines.

B. Dose-Response Analysis

If data on the agent are sufficient to support the parameters of a biologically based model and the purpose of the assessment is such as to justify investing resources supporting its use, this is the preferred approach for both the observed tumor and related response data and for extrapolation below the range of observed data in either animal or human studies.

3.1.3.4 Characterizing Dose-Response Relationships in the Range of Observation and at Low Environmentally Relevant Doses

The first quantitative component in the derivation of AWQC for carcinogens is the dose-response assessment in the range of observation. For most agents, in the absence of adequate data to generate a biologically based model, dose-response relationships in the observed range can be addressed through curve-fitting procedures for response data. It should be noted that the 1999 draft revised cancer guidelines call for modeling of not only tumor data in the observable range, but also other responses thought to be important events preceding tumor development (e.g., DNA adducts, cellular proliferation, receptor binding, hormonal changes). The modeling of these data is intended to better inform the dose-response assessment by providing insights into the relationships of exposure (or dose) below the observable range for tumor response. These non-tumor response data can only play a role in the dose-response assessment if the agent's carcinogenic mode of action is reasonably understood, as well as the role of that precursor event.

The 1999 draft revised cancer guidelines recommend calculating the lower 95 percent confidence limit on a dose associated with an estimated 10 percent increased tumor or relevant non-tumor response (LED_{10}) for quantitative modeling of dose-response relationships in the observed range. The estimate of the LED_{10} is used as the POD for low-dose extrapolations discussed below. This standard point of departure (LED_{10}) is adopted as a matter of science policy to remain as consistent and comparable from case to case as possible. It is also a convenient comparison point for noncancer endpoints. The rationale supporting use of the LED_{10} is that a 10 percent response is at or just below the limit of sensitivity for discerning a statistically significant tumor response in most long-term rodent studies and is within the observed range for other toxicity studies. Use of lower limit takes experimental variability and sample size into account. The ED_{10} (central estimate) is also presented as a reference for comparison uses, especially for use in relative hazard/potency ranking among agents for priority setting.

For some data sets, a choice of the POD other than the LED_{10} may be appropriate. The objective is to determine the lowest reliable part of the dose-response curve for the beginning of the second step of the dose-response assessment—determine the extrapolation range. Therefore, if the observed response is below the LED_{10}, then a lower point may be a better choice (e.g., LED_{5}). Human studies more often support a lower POD than animal studies because of greater sample size.

The POD may be a NOAEL when a margin of exposure analysis is the nonlinear dose-response approach. The kinds of data available and the circumstances of the assessment both contribute to deciding to use a NOAEL or LOAEL which is not as rigorous or as ideal as curve fitting, but can be appropriate. If several data sets for key events and tumor response are available for an agent, and they are a mixture of continuous and incidence data, the most practicable way to assess them together is often through a NOAEL/LOAEL approach.

When an LED value estimated from animal data is used as the POD, it is adjusted to the human equivalent dose using an interspecies dose adjustment or a toxicokinetic analysis as described in Section 3.1.3.3.

Analysis of human studies in the observed range is designed on a case-by-case basis depending on the type of study and how dose and response are measured in the study.

A. Extrapolation to Low, Environmentally Relevant Doses

In most cases, the derivation of an AWQC will require an evaluation of carcinogenic risk at environmental exposure levels substantially lower than those used in the underlying study. Various approaches are used to extrapolate risk outside the range of observed experimental data. In the 1999 draft revised cancer guidelines, the choice of extrapolation method is largely dependent on the mode of action. It should be noted that the term "mode of action" (MOA) is deliberately chosen in the 1999 draft revised cancer guidelines in lieu of the term "mechanism" to indicate using knowledge that is sufficient to draw a reasonable working conclusion without having to know the processes in detail as the term mechanism might imply. The 1999 draft revised cancer guidelines favor the choice of a biologically based model, if the parameters of such models can be calculated from data sources independent of tumor data. It is anticipated that the necessary data for such parameters will not be available for most chemicals. Thus, the 1999 draft revised cancer guidelines allow for several default extrapolation approaches (low-dose linear, nonlinear, or both).

B. Biologically Based Modeling Approaches

If a biologically based approach has been used to characterize the dose-response relationships in the observed range, and the confidence in the model is high, it may be used to extrapolate the dose-response relationship to environmentally relevant doses. For the purposes of deriving AWQC, the environmentally relevant dose would be the risk-specific dose (RSD) associated with incremental lifetime cancer risks in the 10^{-6} to 10^{-4} range for carcinogens for which a linear extrapolation approach is applied.[7] The use of the RSD and the POD/UF to compute the AWQC is presented in Section 3.1.3.5, below. Although biologically-based approaches are appropriate both for characterizing observed dose-response relationships and extrapolating to environmentally relevant doses, it is not expected that adequate data will be available to support the use of such approaches for most substances. In the absence of such data, the default linear approach, the nonlinear (MOE) approach, or both linear and nonlinear approaches will be used.

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[7] For discussion of the cancer risk range, see Section 2.4.

C. Default Linear Extrapolation Approach

The default linear approach replaces the LMS approach that has served as the default for EPA cancer risk assessments. Any of the following conclusions leads to selection of a linear dose-response assessment approach:

- There is an absence of sufficient tumor MOA information.

- The chemical has direct DNA mutagenic reactivity or other indications of DNA effects that are consistent with linearity.

- Human exposure or body burden is high and near doses associated with key events in the carcinogenic process (e.g., 2,3,7,8-tetrachlorodibenzo-p-dioxin).

- Mode of action analysis does not support direct DNA effects, but the dose-response relationship is expected to be linear (e.g., certain receptor-mediated effects).

The procedures for implementing the default linear approach begin with the estimation of a POD as described above. The point of departure, LED_{10}, reflects the interspecies conversion to the human equivalent dose and the other adjustments for less-than-lifetime experimental duration. In most cases, the extrapolation for estimating response rates at low, environmentally relevant exposures is accomplished by drawing a straight line between the POD and the origin (i.e., zero dose, zero extra risk). This is mathematically represented as:

$$y = mx + b$$
$$b = 0$$

(Equation 3-1)

where:

y	=	Response or incidence
m	=	Slope of the line (cancer potency factor) = $^a y / ^a x$
x	=	Dose
b	=	Slope intercept

The slope of the line, "m" (the estimated cancer potency factor at low doses), is computed as:

$$m = \frac{0.10}{LED_{10}}$$

(Equation 3-2)

The RSD is then calculated for a specific incremental targeted lifetime cancer risk (in the range of 10^{-6} to 10^{-4}) as:

$$\text{RSD} = \frac{\text{Target Incremental Cancer Risk}}{m} \qquad \text{(Equation 3-3)}$$

where:

RSD	=	Risk-specific dose (mg/kg-day)
Target Incremental Cancer Risk[8]	=	Value in the range of 10^{-6} to 10^{-4}
m	=	Cancer potency factor (mg/kg-day)$^{-1}$

The use of the RSD to compute the AWQC is described in Section 3.1.3.5 below.

D. Default Nonlinear Approach

As discussed in the 1999 draft revised cancer guidelines, any of the following conclusions leads to a selection of a nonlinear (MOE) approach to dose-response assessment:

- A tumor MOA supporting nonlinearity applies (e.g., some cytotoxic and hormonal agents such as disruptors of hormonal homeostasis), and the chemical does not demonstrate mutagenic effects consistent with linearity.

- An MOA supporting nonlinearity has been demonstrated, and the chemical has some indication of mutagenic activity, but it is judged not to play a significant role in tumor causation.

Thus, a default assumption of nonlinearity is appropriate when there is no evidence for linearity and sufficient evidence to support an assumption of nonlinearity. The MOA may lead to a dose-response relationship that is nonlinear, with response falling much more quickly than linearly with dose, or being most influenced by individual differences in sensitivity. Alternatively, the MOA may theoretically have a threshold (e.g., the carcinogenicity may be a secondary effect of toxicity or of an induced physiological change that is itself a threshold phenomenon).

The nonlinear approach may be used, for instance, in the case of a bladder tumor inducer, where the chemical is not mutagenic and causes only stone formation in male rat bladders at high doses. This dynamic leads to tumor formation only at the high doses. Stone and subsequent tumor formation are not expected to occur at doses lower than those that induce the physiological changes that lead to stone formation. (More detail on this chemical is provided in the cancer section of the Risk Assessment TSD; USEPA, 2000). EPA does not generally try to distinguish between modes of action that might imply a "true threshold" from others with a nonlinear dose-

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[8]In 1980, the target lifetime cancer risk range was set at 10-7 to 10-5. However, both the expert panel for the AWQC workshop (USEPA, 1993) and the peer review workshop experts (USEPA,1999c) recommended that EPA change the risk range to 10-6 to 10-4, to be consistent with SDWA program decisions. See Section 2.4 for more details.

response relationship, because there is usually not sufficient information to distinguish between those possibilities empirically.

The nonlinear MOE approach in the 1986 proposed cancer guidelines compares an observed response rate such as the LED_{10}, NOAEL, or LOAEL with actual or nominal environmental exposures of interest by computing the ratio between the two. In the context of deriving AWQC, the environmentally relevant exposures are nominal targets rather than actual exposures.

If the evidence for an agent indicates nonlinearity (e.g., when carcinogenicity is secondary to another toxicity for which there is a threshold), the MOE analysis for the toxicity is similar to what is done for a noncancer endpoint, and an RfD or RfC for that toxicity may also be estimated and considered in the cancer assessment. However, a threshold of carcinogenic response is not necessarily assumed. It should be noted that for cancer assessment, the MOE analysis begins from a POD that is adjusted for toxicokinetic differences between species to give a human equivalent dose.

To support the use of the MOE approach, risk assessment information provides evaluation of the current understanding of the phenomena that may be occurring as dose (exposure) decreases substantially below the observed data. This gives information about the risk reduction that is expected to accompany a lowering of exposure. The various factors that influence the selection of the UF in an MOE approach are also discussed below.

There are two main steps in the MOE approach. The first step is the selection of a POD. The POD may be the LED_{10} for tumor incidence or a precursor, or in some cases, it may also be appropriate to use a NOAEL or LOAEL value. When animal data are used, the POD is a human equivalent dose or concentration arrived at by interspecies dose adjustment (as discussed in Section 3.1.3.3) or toxicokinetic analysis.

The second step in using MOE analysis to establish AWQC is the selection of an appropriate margin or UF to apply to the POD. This is supported by analyses in the MOE discussion in the risk assessment. The following issues should be considered when establishing the overall UF for the derivation of AWQC using the MOE approach (others may be found appropriate in specific cases):

•   The nature of the response used for the dose-response assessment, for instance, whether it is a precursor effect or a tumor response. The latter may support a greater MOE.

•   The slope of the observed dose-response relationship at the POD and its uncertainties and implications for risk reduction associated with exposure reduction. (A steeper slope implies a greater reduction in risk as exposure decreases. This may support a smaller MOE).

•   Human sensitivity compared with that of experimental animals.

•   Nature and extent of human variability and sensitivity.

•   Human exposure. The MOE evaluation also takes into account the magnitude, frequency, and duration of exposure. If the population exposed in a particular scenario is wholly or largely composed of a subpopulation of special concern (e.g., children) for whom evidence indicates a special sensitivity to the agent's MOA, an adequate MOE would be larger than for general population exposure.

E. Both Linear and Nonlinear Approaches

Any of the following conclusions leads to selection of both a linear and nonlinear approach to dose-response assessment. Relative support for each dose-response method and advice on the use of that information needs to be documented for the AWQC. In some cases, evidence for one MOA is stronger than for the other, allowing emphasis to be placed on that dose-response approach. In other cases, both modes of action are equally possible, and both dose-response approaches should be emphasized.

C   Modes of action for a single tumor type support both linear and nonlinear dose response in different parts of the dose-response curve (e.g., 4,4' methylene chloride).

C   A tumor mode of action supports different approaches at high and low doses; e.g., at high dose, nonlinearity, but, at low dose, linearity (e.g., formaldehyde).

C   The agent is not DNA-reactive and all plausible modes of action are consistent with nonlinearity, but not fully established.

C   Modes of action for different tumor types support differing approaches, e.g., nonlinear for one tumor type and linear for another due to lack of MOA information (e.g., trichloroethylene).

3.1.3.5 AWQC Calculation

A. Linear Approach

The following equation is used for the calculation of the AWQC for carcinogens where an RSD is obtained from the linear approach:

$$AWQC \ = \ RSD \ \cdot \ \left(\frac{BW}{DI \ + \ \sum_{i=2}^{4} (FI_i \ \cdot \ BAF_i)} \right)$$ (Equation 3-4)

AWQC = Ambient water quality criterion (mg/L)
RSD   = Risk-specific dose (mg/kg-day)
BW   = Human body weight (kg)
DI   = Drinking water intake (L/day)
FI_i = Fish intake at trophic level I (I = 2, 3, and 4) (kg/day)
BAF_i = Bioaccumulation factor for trophic level I (I = 2, 3, and 4), lipid
         normalized (L/kg)

B. Nonlinear Approach

In those cases where the nonlinear, MOE approach is used, a similar equation is used to calculate the AWQC [9]

$$AWQC = \frac{POD}{UF} \cdot RSC \cdot \left(\frac{BW}{DI + \sum_{i=2}^{4} (FI_i \cdot BAF_i)} \right)$$
                  (Equation 3-5)

where variables are defined as for Equation 3-4 and:

POD   = Point of departure (mg/kg-day)
UF   = Uncertainty factor (unitless)
RSC   = Relative source contribution (percentage or subtraction)

Differences between the AWQC values obtained using the linear and nonlinear approaches should be noted. First, the AWQC value obtained using the default linear approach corresponds to a specific estimated incremental lifetime cancer risk level in the range of 10^{-4} to 10^{-6}. In contrast, the AWQC obtained using the nonlinear approach does not describe a specific cancer risk. The AWQC calculations shown above are appropriate for waterbodies that are used as sources of drinking water.

The actual AWQC chosen for the protection of human health is based on a review of all relevant information, including cancer and noncancer data. The AWQC may, or may not, utilize the value obtained from the cancer analysis in the final AWQC value. The endpoint selected for the AWQC will be based on consideration of the weight of evidence and a complete analysis of all toxicity endpoints.

3.1.3.6 Risk Characterization

Risk assessment is an integrative process that is documented in a risk characterization summary. Risk characterization is the final step of the risk assessment process in which all

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[9] Although appearing in this equation as a factor to be multiplied, the RSC can also be an amount subtracted.

preceding analyses (i.e., hazard, dose-response, and exposure assessments) are tied together to convey the overall conclusions about potential human risk. This component of the risk assessment process characterizes the data in nontechnical terms, explaining the extent and weight of evidence, major points of interpretation and rationale, and strengths and weaknesses of the evidence, and discussing alternative approaches, conclusions, uncertainties, and variability that deserve serious consideration.

Risk characterization information accompanies the numerical AWQC value and addresses the major strengths and weaknesses of the assessment arising from the availability of data and the current limits of understanding the process of cancer causation. Key issues relating to the confidence in the hazard assessment and the dose-response analysis (including the low-dose extrapolation procedure used) are discussed. Whenever more than one interpretation of the weight of evidence for carcinogenicity or the dose-response characterization can be supported, and when choosing among them is difficult, the alternative views are provided along with the rationale for the interpretation chosen in the derivation of the AWQC value. Where possible, quantitative uncertainty analyses of the data are provided; at a minimum, a qualitative discussion of the important uncertainties is presented.

3.1.3.7 Use of Toxicity Equivalence Factors and Relative Potency Estimates

The 1999 draft revised cancer guidelines state:

A toxicity equivalence factor (TEF) procedure is one used to derive quantitative dose-response estimates for agents that are members of a category or class of agents. TEFs are based on shared characteristics that can be used to order the class members by carcinogenic potency when cancer bioassay data are inadequate for this purpose. The ordering is by reference to the characteristics and potency of a well-studied member or members of the class. Other class members are indexed to the reference agent(s) by one or more shared characteristics to generate their TEFs.

In addition, the 1999 draft revised cancer guidelines state that TEFs are generated and used for the limited purpose of assessment of agents or mixtures of agents in environmental media when better data are not available. When better data become available for an agent, the TEF should be replaced or revised. To date, adequate data to support use of TEFs have been found only for dibenzofurans (dioxins) and coplanar polychlorinated biphenyls (PCBs) (USEPA, 1989, 1999b).

The uncertainties associated with TEFs must be described when this approach is used. This is a default approach to be used when tumor data are not available for individual components in a mixture. Relative potency factors (RPFs) can be similarly derived and used for agents with carcinogenicity or other supporting data. The RPF is conceptually similar to TEFs, but does not have the same level of data to support it and thus has a less rigorous definition compared with the TEF. TEFs and RPFs are used only when there is no better alternative. When they are used, assumptions and uncertainties associated with them are discussed. As of today, there are only

three classes of compounds for which relative potency approaches have been examined by EPA: dibenzofurans (dioxins), polychlorinated biphenyls (PCBs), and polycyclic aromatic hydrocarbons (PAHs). There are limitations to the use of TEF and RFP approaches, and caution should be exercised when using them. More guidance can be found in the draft document for conducting health risk assessment of chemical mixtures, published by the EPA Risk Assessment Forum (USEPA,1999b).

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3.2   NONCANCER EFFECTS

3.2.1   1980 AWQC National Guidelines for Noncancer Effects

In the 1980 AWQC National Guidelines, the Agency evaluated noncancer human health effects from exposure to chemical contaminants using Acceptable Daily Intake (ADI) levels. ADIs were calculated by dividing NOAELs by safety factors (SFs) to obtain estimates of doses of chemicals that would not be expected to cause adverse effects over a lifetime of exposure. In accordance with the National Research Council report of 1977 (NRC, 1977), EPA used SFs of 10, 100, or 1,000, depending on the quality and quantity of the overall database. In general, a factor of 10 was suggested when good-quality data identifying a NOAEL from human studies were available. A factor of 100 was suggested if no human data were available, but the database contained valid chronic animal data. For chemicals with no human data and scant animal data, a factor of 1,000 was recommended. Intermediate SFs could also be used for databases that fell between these categories.

AWQC were calculated using the ADI levels together with standard exposure assumptions about the rates of human ingestion of water and fish, and also accounting for intake from other sources (see Equation 1-1 in the Introduction). Surface water concentrations at or below the calculated criteria concentrations would be expected to result in human exposure levels at or

below the ADI. Inherent in these calculations is the assumption that, generally, adverse effects from noncarcinogens exhibit a threshold.

3.2.2 Noncancer Risk Assessment Developments Since 1980

Since 1980, the risk assessment of noncarcinogenic chemicals has changed. To remove the value judgments implied by the words "acceptable" and "safety," the ADI and SF terms have been replaced with the terms RfD and UF/modifying factor (MF), respectively.

For the risk assessment of general systemic toxicity, the Agency currently uses the guidelines contained in the IRIS background document entitled *Reference Dose (RfD): Description and Use in Health Risk Assessments* (hereafter the "IRIS background document". That document defines an RfD as "an estimate (with uncertainty spanning approximately an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious effects over a lifetime" (USEPA, 1993a). The most common approach for deriving the RfD does not involve dose-response modeling. Instead, an RfD for a given chemical is usually derived by first identifying the NOAEL for the most sensitive known toxicity endpoint, that is, the toxic effect that occurs at the lowest dose. This effect is called the critical effect. Factors such as the study protocol, the species of experimental animal, the nature of the toxicity endpoint assessed and its relevance to human effects, the route of exposure, and exposure duration are critically evaluated in order to select the most appropriate NOAEL from among all available studies in the chemical's database. If no appropriate NOAEL can be identified from any study, then the LOAEL for the critical effect endpoint is used and an uncertainly factor for LOAEL-to-NOAEL extrapolation is applied. Using this approach, the RfD is equal to the NOAEL (or LOAEL) divided by the product of UFs and, occasionally, an MF:

$$\text{RfD (mg/kg/day)} = \frac{\text{NOAEL (or LOAEL)}}{\text{UF} \cdot \text{MF}} \qquad \text{(Equation 3-6)}$$

The definitions and guidance for use of the UFs and the MFs are provided in the IRIS background document and are repeated in Table 3-1.

The IRIS background document on the RfD (USEPA, 1993a) provides guidance for critically assessing noncarcinogenic effects of chemicals and for deriving the RfD. Another reference on this topic is Dourson (1994). Furthermore, the Agency has also published separate guidelines for assessing specific toxic endpoints, such as developmental toxicity (USEPA, 1991a), reproductive toxicity (USEPA, 1996a), and neurotoxicity risk assessment (USEPA, 1995). These endpoint-specific guidelines will be used for their respective areas in the hazard assessment step and will complement the overall toxicological assessment. It should be noted, however, that an RfD, derived using the most sensitive known endpoint, is considered protective against all noncarcinogenic effects.

TABLE 3-1. UNCERTAINTY FACTORS AND THE MODIFYING FACTOR

Uncertainty Factor	Definition
UF_H	Use a 1, 3, or 10-fold factor when extrapolating from valid data in studies using long-term exposure to average healthy humans. This factor is intended to account for the variation in sensitivity (intraspecies variation) among the members of the human population.
UF_A	Use an additional factor of 1, 3, or 10 when extrapolating from valid results of long-term studies on experimental animals when results of studies of human exposure are not available or are inadequate. This factor is intended to account for the uncertainty involved in extrapolating from animal data to humans (interspecies variation).
UF_S	Use an additional factor of 1, 3, or 10 when extrapolating from less-than-chronic results on experimental animals when there are no useful long-term human data. This factor is intended to account for the uncertainty involved in extrapolating from less-than-chronic NOAELs to chronic NOAELs.
UF_L	Use an additional factor of 1, 3, or 10 when deriving an RfD from a LOAEL, instead of a NOAEL. This factor is intended to account for the uncertainty involved in extrapolating from LOAELs to NOAELs.
UF_D	Use an additional 3- or 10-fold factor when deriving an RfD from an "incomplete" database. This factor is meant to account for the inability of any single type of study to consider all toxic endpoints. The intermediate factor of 3 (approximately ½ $\log_{10}$ unit, i.e., the square root of 10) is often used when there is a single data gap exclusive of chronic data. It is often designated as UF_D.

Modifying Factor

Use professional judgment to determine the MF, which is an additional uncertainty factor that is greater than zero and less than or equal to 10. The magnitude of the MF depends upon the professional assessment of scientific uncertainties of the study and database not explicitly treated above (e.g., the number of species tested). The default value for the MF is 1.

Note: With each UF or MF assignment, it is recognized that professional scientific judgment must be used. The total product of the uncertainty factors and modifying factor should not exceed 3,000.

Similar to the procedure used in the 1980 AWQC National Guidelines, the revised method of deriving AWQC for noncarcinogens uses the RfD together with various assumptions concerning intake of the contaminant from both water and non-water sources of exposure. The objective of an AWQC for noncarcinogens is to ensure that human exposure to a substance related to its presence in surface water, combined with exposure from other sources, does not exceed the RfD. The algorithm for deriving AWQC for noncarcinogens using the RfD is presented as Equation 1-1 in the Introduction.

3.2.3   Issues and Recommendations Concerning the Derivation of AWQC for Noncarcinogens

During a review of the 1980 AWQC National Guidelines (USEPA, 1993b), the Agency identified several issues that must be resolved in order to develop a final revised methodology for deriving AWQC based on noncancer effects. These issues, as discussed below, mainly concern the derivation of the RfD as the basis for such an AWQC. Foremost among these issues is whether the Agency should revise the present method or adopt entirely new procedures that use quantitative dose-response modeling for the derivation of the RfD. Other issues include the following:

- Presenting the RfD as a single point value or as a range to reflect the inherent imprecision of the RfD;

- Selecting specific guidance documents for derivation of noncancer health effect levels;

- Considering severity of effect in the development of the RfD;

- Using less-than-90-day studies as the basis for RfDs;

- Integrating reproductive/developmental, immunotoxicity, and neurotoxicity data into the RfD calculation;

- Applying toxicokinetic data in risk assessments; and

- Considering the possibility that some noncarcinogenic effects do not exhibit a threshold.

3.2.3.1   Using the Current NOAEL/UF-Based RfD Approach or Adopting More Quantitative Approaches for Noncancer Risk Assessment

The current NOAEL/UF-based RfD methodology, or its predecessor ADI/SF methodology, have been used since 1980. This approach assumes that there is a threshold exposure below which adverse noncancer health effects are not expected to occur. Exposures above this threshold are believed to pose some risk to exposed individuals; however, the current approach does not address the nature and magnitude of the risk above the threshold level (i.e., the shape of the dose-response curve above the threshold). The NOAEL/UF-based RfD approach is

intended primarily to ensure that the RfD value derived from the available data falls below the population effects threshold. However, the NOAEL/UF-based RfD procedure has limitations. In particular, this method requires that one of the actual experimental doses used by the researchers in the critical study be selected as the NOAEL or LOAEL value. The determination that a dose is a NOAEL or LOAEL will depend on the biological endpoints used and the statistical significance of the data. Statistical significance will depend on the number and spacing of dose groups and the numbers of animals used in each dose group. Studies using a small number of animals can limit the ability to distinguish statistically significant differences among measurable responses seen in dose groups and control groups. Furthermore, the determination of the NOAEL or LOAEL also depends on the dose spacing of the study. Doses are often widely spaced, typically differing by factors of three to ten. A study can identify a NOAEL and a LOAEL from among the doses studied, but the "true" effects threshold cannot be determined from those results. The study size and dose spacing limitations also limit the ability to characterize the nature of the expected response to exposures between the observed NOAEL and LOAEL values.

The limitations of the NOAEL/UF approach have prompted development of alternative approaches that incorporate more quantitative dose-response information. The traditional NOAEL approach for noncancer risk assessment has often been a source of controversy and has been criticized in several ways. For example, experiments involving fewer animals tend to produce higher NOAELs and, as a consequence, may produce higher RfDs. Larger sample sizes, on the other hand, should provide greater experimental sensitivity and lower NOAELs. The focus of the NOAEL approach is only on the dose that is the NOAEL, and the NOAEL must be one of the experimental doses. It also ignores the shape of the dose-response curve. Thus, the slope of the dose-response plays little role in determining acceptable exposures for human beings. Therefore, in addition to the NOAEL/UF-based RfD approach described above, EPA will accept other approaches that incorporate more quantitative dose-response information in appropriate situations for the evaluation of noncancer effects and the derivation of RfDs. However, the Agency wishes to emphasize that it still believes the NOAEL/UF RfD methodology is valid and can continue to be used to develop RfDs.

Two alternative approaches that may have relevance in assisting in the derivation of the RfD for a chemical are the BMD and the categorical regression approaches. These alternative approaches may overcome some of the inherent limitations in the NOAEL/UF approach. For example, the BMD analyses for developmental effects show that NOAELs from studies correlate well with a 5 percent response level (Allen et al., 1994). The BMD and the categorical regression approaches usually have greater data requirements than the RfD approach. Thus, it is unlikely that any one approach will apply to every circumstance; in some cases, different approaches may be needed to accommodate the varying databases for the range of chemicals for which water quality criteria must be developed. Acceptable approaches will satisfy the following criteria: (1) meet the appropriate risk assessment goal; (2) adequately describe the toxicity database and its quality; (3) characterize the endpoints properly; (4) provide a measure of the quality of the "fit" of the model when a model is used for dose-response analysis; and (5) describe the key assumptions and uncertainties.

A. The Benchmark Dose

The BMD is defined as the dose estimated to produce a predetermined level of change in response (the Benchmark Response level, or BMR) relative to control. The BMDL is defined as the statistical lower confidence limit on the BMD. In the derivation of an RfD, the BMD is used as the dose to which uncertainty factors are applied instead of the NOAEL. The BMD approach first models a dose-response curve for the critical effect(s) using available experimental data. Several mathematical algorithms can be used to model the dose-response curve, such as polynomial or Weibull functions. To define a BMD from the modeled curve for quantal data, the assessor first selects the BMR. The choice of the BMR is critical. For quantal endpoints, a particular level of response is chosen (e.g., 1 percent, 5 percent, or 10 percent). For continuous endpoints, the BMR is the degree of change from controls and is based on what is considered a biologically significant change. The BMD is derived from the BMR dose by applying the desired confidence limit calculation. The RfD is obtained by dividing the BMD by one or more uncertainty factors, similar to the NOAEL approach. Because the BMD is used like the NOAEL to obtain the RfD, the BMR should be selected at or near the low end of the range of increased risks that can be detected in a study of typical size. Generally, this falls in the range between the ED_{01} and the ED_{10}.

The Agency will accept use of a BMD approach to derive RfDs for those agents for which there is an adequate database. There are a number of technical decisions associated with the application of the BMD technique. These include the following:

- The definition of an adverse response;

- Selection of response data to model;

- The form of the data used (continuous versus quantal);

- The choice of the measures of increased risk (extra risk versus additional risk);

- The choice of mathematical model (including use of nonstandard models for unusual data sets);

- The selection of the BMR;

- Methods for calculating the confidence interval;

- Selection of the appropriate BMD as the basis for the RfD (when multiple endpoints are modeled from a single study, when multiple models are applied to a single response, and when multiple BMDs are calculated from different studies); and

- The use of uncertainty factors with the BMD approach.

These topics are discussed in detail in Crump et al. (1995) and in the Risk Assessment TSD Volume (USEPA, 2000). The use of the BMD approach has been discussed in general terms by several authors (Gaylor, 1983; Crump, 1984; Dourson et al., 1985; Kimmel and Gaylor, 1988; Brown and Erdreich, 1989; Kimmel, 1990). The International Life Sciences Institute (ILSI) also held a major workshop on the BMD in September 1993; the workshop proceedings are summarized in ILSI (1993) and in Barnes et al. (1995). For further information on these technical issues, the reader is referred to the publications referenced above.

The BMD approach addresses several of the quantitative or statistical criticisms of the NOAEL approach. These are discussed at greater length in Crump et al. (1995) and are summarized here. First, the BMD approach uses all the dose-response information in the selected study rather than just a single data point, such as the NOAEL or LOAEL. By using response data from all of the dose groups to model a dose-response curve, the BMD approach allows for consideration of the steepness of the slope of the curve when estimating the ED_{10}. The use of the full data set also makes the BMD approach less sensitive to small changes in data than the NOAEL approach, which relies on the statistical comparison of individual dose groups. The BMD approach also allows consistency in the consideration of the level of effect (e.g., a 10 percent response rate) across endpoints.

The BMD approach accounts more appropriately for the size of each dose group than the NOAEL approach. Laboratory tests with fewer animals per dose group tend to yield higher NOAELs, and thus higher RfDs, because statistically significant differences in response rates are harder to detect. Therefore, in the NOAEL approach, dose groups with fewer animals lead to a higher (less conservative) RfD. In contrast, with the BMD approach, smaller dose groups will tend to have the effect of extending the confidence interval around the ED_{10}; therefore, the lower confidence limit on the ED_{10} (the BMD) will be lower. With the BMD approach, greater uncertainty (smaller test groups) leads to a lower (more conservative) RfD.

There are some issues to be resolved before the BMD approach is used routinely. These were identified in a 1996 Peer Consultation Workshop (USEPA, 1996b). Methods for routine use of the BMD are currently under development by EPA. Several RfCs and RfDs based on the BMD approach are included in EPA's IRIS database. These include reference values for methylmercury based on delayed postnatal development in humans; carbon disulfide based on neurotoxicity; 1,1,1,2-tetrafluoroethane based on testicular effects in rats; and antimony trioxide based on chronic pulmonary interstitial inflammation in female rats.

Various mathematical approaches have been proposed for modeling developmental toxicity data (e.g., Crump, 1984; Kimmel and Gaylor, 1988; Rai and Van Ryzin, 1985; Faustman et al., 1989), which could be used to calculate a BMD. Similar methods can be used to model other types of toxicity data, such as neurotoxicity data (Gaylor and Slikker, 1990, 1992; Glowa and MacPhail, 1995). The choice of the mathematical model may not be critical, as long as estimation is within the observed dose range. Since the model fits a mathematical equation to the observed data, the assumptions in a particular model regarding the existence or absence of a threshold for the effect may not be pertinent (USEPA, 1997). Thus, any model that suitably fits

the empirical data is likely to provide a reasonable estimate of a BMD. However, research has shown that flexible models that are nonsymmetric (e.g., the Weibull) are superior to symmetric models (e.g., the probit) in estimating the BMD because the data points at the higher doses have less influence on the shape of the curve than at low doses. In addition, models should incorporate fundamental biological factors where such factors are known (e.g., intralitter correlation for developmental toxicity data) in order to account for as much variability in the data as possible. The Agency is currently using the BMD approach in risk assessments where the data support its use. Draft guidelines for application of the BMD approach also are being developed by the Agency.

Use of BMD methods involves fitting mathematical models to dose-response data obtained primarily from toxicology studies. When considering available models to use for a BMD analysis, it is important to select the model that fits the data the best and is the most biologically appropriate. EPA has developed software following several years of research and development, expert peer review, public comment, subsequent revision, and quality assurance testing. The software (BMDS, Version 1.2) can be downloaded from http://www.epa.gov/ncea/bmds.htm. BMDS facilitates these operations by providing simple data-management tools, a comprehensive help manual, an online help system, and an easy-to-use interface to run multiple models on the same dose-response data.

As part of this software package, EPA has included sixteen (16) different models that are appropriate for the analysis of dichotomous (quantal) data (Gamma, Logistic, Log-Logistic, Multistage, Probit, Log-Probit, Quantal-Linear, Quantal-Quadratic, Weibull), continuous data (Linear, Polynomial, Power, Hill), and nested developmental toxicology data (NLogistic, NCTR, Rai & Van Ryzin). Results from all models include a reiteration of the model formula and model run options chosen by the user, goodness-of-fit information, the BMD, and the estimate of the lower-bound confidence limit on the benchmark dose (BMDL). Model results are presented in textual and graphical output files which can be printed or saved and incorporated into other documents.

B. *Categorical Regression*

Categorical regression is an emerging technique that may have relevance for the derivation of RfDs or for estimating risk above the RfD (Dourson et al., 1997; Guth et al., 1997). The categorical regression approach, like the BMD approach, can be used to estimate a dose that corresponds to a given probability of adverse effects. This dose would then be divided by UFs to establish an RfD. However, unlike the BMD approach, the Categorical regression approach can incorporate information on different health endpoints in a single dose-response analysis. For those health effects for which studies exist, responses to the substance in question are grouped into severity categories; for example (1) no effect, (2) no adverse effect, (3) mild-to-moderate adverse effect, and (4) frank effect. These categories correspond to the dose categories currently used in setting the RfD, namely, the no-observed-effect level (NOEL), NOAEL, LOAEL, and frank-effect level (FEL), respectively. Logistic transformation or other applicable mathematical operations are used to model the probability of experiencing effects in a certain category as a

function of dose (Harrell, 1986; Hertzberg, 1989). The "acceptability" of the fit of the model to the data can be judged using several statistical measures, including the P^2 statistic, correlation coefficients, and the statistical significance of its model parameter estimates.

The resulting mathematical equation can be used to find a dose (or the lower confidence bound on the dose) at which the probability of experiencing adverse effects does not exceed a selected level, e.g., 10 percent. This dose (like the NOAEL or BMD) would then be divided by relevant UFs to calculate an RfD. For more detail on how to employ the categorical regression approach, see the discussion in the Risk Assessment TSD (USEPA, 2000).

As with the BMD approach, the categorical regression approach has the advantage of using more of the available dose-response data to account for response variability as well as accounting for uncertainty due to sample size through the use of confidence intervals. Additional advantages of categorical regression include the combining of data sets prior to modeling, thus allowing the calculation of the slope of a dose-response curve for multiple adverse effects rather than only one effect at a time. Another advantage is the ability to estimate risks for different levels of severity from exposures above the RfD.

On the other hand, as with BMD, opinions differ over the amount and adequacy of data necessary to implement the method. The categorical regression approach also requires judgments regarding combining data sets, judging goodness-of-fit, and assigning severity to a particular effect. Furthermore, this approach is still in the developmental stage. It is not recommended for routine use, but may be used when data are available and justify the extensive analyses required.

C. Summary

Whether a NOAEL/UF-based methodology, a BMD, a categorical regression model, or other approach is used to develop the RfD, the dose-response-evaluation step of a risk assessment process should include additional discussion about the nature of the toxicity data and its applicability to human exposure and toxicity. The discussion should present the range of doses that are effective in producing toxicity for a given agent; the route, timing, and duration of exposure; species specificity of effects; and any toxicokinetic or other considerations relevant to extrapolation from the toxicity data to human-health-based AWQC. This information should always accompany the characterization of the adequacy of the data.

3.2.3.2 Presenting the RfD as a Single Point or as a Range for Deriving AWQC

Although the RfD has traditionally been presented and used as a single point, its definition contains the phrase ". . . an estimate (with uncertainty spanning perhaps an order of magnitude) . . ." (USEPA, 1993a). Underlying this concept is the reasoning that the selection of the critical effect and the total uncertainty factor used in the derivation of the RfD is based on the "best" scientific judgment, and that competent scientists examining the same database could derive RfDs which varied within an order of magnitude.

In one instance, IRIS presented the RfD as a point value within an accompanying range. EPA derived a single number as the RfD for arsenic (0.3：g/kg-day), but added that "strong scientific arguments can be made for various values within a factor of 2 or 3 of the currently recommended RfD value, i.e., 0.1 to 0.8 ：g/kg/day" (USEPA, 1993c). EPA noted that regulatory managers should be aware of the flexibility afforded them through this action.

There are situations in which the risk manager can select an alternative value to use in place of the RfD in the AWQC calculations. The domain from which this alternative value can be selected is restricted to a defined range around the point estimate. As explained further below, the Agency is recommending that sometimes the use of a value other than the calculated RfD point estimate is appropriate in characterizing risk. The selection of an alternative value within an appropriate range must be determined for each individual situation, since several factors affect the selection of the alternative value. Observing similar effects in several animal species, including humans, can increase confidence in the selection of the critical effect and thereby narrow the range of uncertainty. There are other factors that can affect the precision. These include the slope of the dose-response curve, seriousness of the observed effect, dose spacing, and possibly the route for the experimental doses. Dose spacing and the number of animals in the study groups used in the experiment can also affect the confidence in the RfD.

To derive the AWQC, the calculated point estimate of the RfD is the default. Based on consideration of the available data, the use of another number within the range defined by the product of the UF(s) (and MF, if used) could be justified in some specific situations. This means that there are risk considerations which indicate that some value in the range other than the point estimate may be more appropriate, based on human health or environmental fate considerations. For example, the bioavailability of the contaminant in fish tissues is one factor to consider. If bioavailability from fish tissues is much lower than that from water and the RfD was derived from a study in which the contaminant exposure was from drinking water, the alternative to the calculated RfD could be selected from the high end of the range and justified using the quantitative difference in bioavailability.

Most inorganic contaminants, particularly divalent cations, have bioavailability values of 20 percent or less from a food matrix, but are much more available (about 80 percent or higher) from drinking water. Accordingly, the external dose necessary to produce a toxic internal dose would likely be higher for a study where the exposure occurred through the diet rather than the drinking water. As a result, the RfD from a dietary study would likely be higher than that for the drinking water study if equivalent external doses had been used. Conversely, in cases where the NOAEL that was the basis for the RfD came from a dietary study, the alternative value could be slightly lower than the calculated RfD.

Because the uncertainty around the dose-response relationship increases as extrapolation below the observed data increases, the use of an alternative point within the range may be more appropriate in characterizing the risk than the use of the calculated RfD, especially in situations when the uncertainty is high. Therefore, as a matter of policy, the 2000 Human Health Methodology permits the selection of a single point within a range about the calculated RfD to be

used as the basis of the AWQC if an adequate justification of the alternative point is provided. More complete discussion of this option, including limitations on the span of the range, is provided in the Risk Assessment TSD (USEPA, 2000).

3.2.3.3 Guidelines to be Adopted for Derivation of Noncancer Health Effects Values

The Agency currently is using the IRIS background document as the general basis for the risk assessment of noncarcinogenic effects of chemicals (USEPA, 1993a). EPA recommends continued use of this document for this purpose. However, it should be noted that the process for evaluating chemicals for inclusion in IRIS is undergoing revision (USEPA, 1996c). The revised assessments for many chemicals are now available on IRIS and can be consulted as examples of the RfD development process and required supporting documentation.

3.2.3.4 Treatment of Uncertainty Factors/Severity of Effects During the RfD Derivation and Verification Process

During the RfD derivation and toxicology review process, EPA considers the uncertainty in extrapolating between animal species and within individuals of a species, as well as specific uncertainties associated with the completeness of the database. The Agency's RfD Work Group has always considered the severity of the observed effects induced by the chemical under review when choosing the value of the UF with a LOAEL. For example, during the derivation and verification of the RfD for zinc (USEPA, 1992), an uncertainty factor less than the standard factor of 10 (UF of 3) was assigned to the relatively mild decrease in erythrocyte superoxide dismutase activity in human subjects. EPA recommends that the severity of the critical effect be assessed when deriving an RfD and that risk managers be made aware of the severity of the effect and the weight placed on this attribute of the effect when the RfD was derived.

3.2.3.5 Use of Less-Than-90-Day Studies to Derive RfDs

Generally, less-than-90-day experimental studies are not used to derive an RfD. This is based on the rationale that studies lasting for less than 90 days may be too short to detect various toxic effects. However, EPA, has in certain circumstances, derived an RfD based on a less-than-90-day study. For example, the RfD for nonradioactive effects of uranium is based on a 30-day rabbit study (USEPA, 1989). The short-term exposure period was used, because it was adequate for determining doses that cause chronic toxicity. In other cases, it may be appropriate to use a less-than-90-day study because the critical effect is expressed in less than 90 days. For example, the RfD for nitrate was derived and verified using studies that were less than 3-months in duration (USEPA, 1991b). For nitrate, the critical effect of methemoglobinemia in infants occurs in less than 90 days. When it can be demonstrated from other data in the toxicological database that the critical adverse effect is expressed within the study period and that a longer exposure duration would not exacerbate the observed effect or cause the appearance of some other adverse effect, the Agency may choose to use less-than-90-day studies as the basis of the RfD. Such values would have to be used with care because of the uncertainty in determining if other effects might be expressed if exposure was of greater duration than 90 days.

3.2.3.6 Use of Reproductive/Developmental, Immunotoxicity, and Neurotoxicity Data as the Basis for Deriving RfDs

All relevant toxicity data have some bearing on the RfD derivation and verification and are considered by EPA. The "critical" effect is the adverse effect most relevant to humans or, in the absence of an effect known to be relevant to humans, the adverse effect that occurs at the lowest dose in animal studies. If the critical effect is neurotoxicity, EPA will use that endpoint as the basis for the derivation and verification of an RfD, as it did for the RfD for acrylamide. Moreover, the Agency is continually revising its procedures for noncancer risk assessment. For example, EPA has released guidelines for deriving developmental RfDs (RfD$_{DT}$, USEPA, 1991a), for using reproductive toxicity (USEPA, 1996a), and neurotoxicity (USEPA, 1995) data in risk assessments. The Agency is currently working on guidelines for using immunotoxicity data to derive RfDs. In addition, the Agency is proceeding with the process of generating acceptable emergency health levels for hazardous substances in acute exposure situations based on established guidelines (NRC, 1993).

3.2.3.7 Applicability of Toxicokinetic Data in Risk Assessment

All pertinent toxicity data should be used in the risk assessment process, including toxicokinetic and mechanistic data. The Agency has used toxicokinetic data in deriving the RfD for cadmium and other compounds and currently is using toxicokinetic data to better characterize human inhalation exposures from animal inhalation experiments during derivation/verification of RfCs. In analogy to the RfD, the RfC is considered to be an estimate of a concentration in the air that is not anticipated to cause adverse noncancer effects over a lifetime of inhalation exposure (USEPA, 1994; Jarabek, 1995a). For RfCs, different dosimetry adjustments are made to account for the differences between laboratory animals and humans in gas uptake and disposition or in particle clearance and retention. This procedure results in calculation of a "human equivalent concentration." Based on the use of these procedures, an interspecies UF of 3 (i.e., approximately $10^{0.5}$), instead of the standard factor of 10, is used in the RfC derivation (Jarabek, 1995b).

Toxicokinetics and toxicodynamics of a chemical each contribute to a chemical's observed toxicity, and specifically, to observed differences among species in sensitivity. Toxicokinetics describes the disposition (i.e., deposition, absorption, distribution, metabolism, and elimination of chemicals in the body) and can be approximated using toxicokinetic models. Toxicodynamics describes the toxic interaction of the agent with the target cell. In the absence of specific data on their relative contributions to the toxic effects observed in species, each is considered to account for approximately one-half of the difference in observed effects for humans compared with laboratory animals. The implication of this assumption is that an interspecies uncertainty factor of 3 rather than 10 could be used for deriving an RfD when valid toxicokinetic data and models can be applied to obtain an oral "human equivalent applied dose" (Jarabek, 1995b). If specific data exist on the relative contribution of either element to observed effects, that proportion will be used. The role exposure duration may play, and whether or not the chemical or its damage may

accumulate over time in a particular scenario, also requires careful consideration (Jarabek, 1995c).

3.2.3.8 Consideration of Linearity (or Lack of a Threshold) for Noncarcinogenic Chemicals

It is quite possible that there are chemicals with noncarcinogenic endpoints that have no threshold for effects. For example, in the case of lead, it has not been possible to identify a threshold for effects on neurological development. Other examples could include genotoxic teratogens and germline mutagens. Genotoxic teratogens act by causing mutational events during organogenesis, histogenesis, or other stages of development. Germline mutagens interact with germ cells to produce mutations which may be transmitted to the zygote and expressed during one or more stages of development. However, there are few chemicals which currently have sufficient mechanistic information about these possible modes of action. It should be recognized that although an MOA consistent with linearity is possible (especially for agents known to be mutagenic), this has yet to be reasonably demonstrated for most toxic endpoints other than cancer.

EPA has recognized the potential for nonthreshold noncarcinogenic endpoints and discussed this issue in the *Guidelines for Developmental Toxicity Risk Assessment* (USEPA, 1991a) and in the 1986 *Guidelines for Mutagenicity Risk Assessment* (USEPA, 1986). An awareness of the potential for such teratogenic/mutagenic effects should be established in order to deal with such data. However, without adequate data to support a genetic or mutational basis for developmental or reproductive effects, the default becomes a UF or MOA approach, which are procedures utilized for noncarcinogens assumed to have a threshold. Therefore, genotoxic teratogens and germline mutagens should be considered an exception while the traditional uncertainty factor approach is the general rule for calculating criteria or values for chemicals demonstrating developmental/reproductive effects. For the exceptional cases, since there is no well-established mechanism for calculating criteria protective of human health from the effects of these agents, criteria will be established on a case-by-case basis. Other types of nonthreshold noncarcinogens must also be handled on a case-by-case basis.

3.2.3.9 Minimum Data Guidance

For details on minimum data guidance for RfD development, see the Risk Assessment TSD (USEPA, 2000).

3.2.4 References for Noncancer Effects

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